PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference JE/P/237/WOD	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/GB2004/004460	International filing date *(day/month/year)* 21.10.2004	Priority date *(day/month/year)* 21.10.2003
International Patent Classification (IPC) or national classification and IPC A61K47/02, A61K9/18		
Applicant PSIMEDICA LIMITED		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 6 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☒ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention .
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01.08.2005	21.02.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Vermeulen, S Telephone No. +49 89 2399-7520

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/004460

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-39 as originally filed

Claims, Numbers

1-41 received on 27.12.2005 with letter of 22.12.2005

Drawings, Sheets

1/18-18/18 as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☒ the claims, Nos. 1
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 16,17,37-41

because:

☒ the said international application, or the said claims Nos. 16,17,37-41 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2,11,18-36
	No:	Claims	1,3-10,12-17,37-41
Inventive step (IS)	Yes:	Claims	2
	No:	Claims	1,3-41
Industrial applicability (IA)	Yes:	Claims	1-15,18-36
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (SEPARATE SHEET)

International application No.
PCT/GB2004/004460

Re Item I
Basis of the report

The amendments filed with the letter dated 22 December 2005 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT. As a consequence, this report has been established as if the amendments have not been made. The amendments concerned are the following:

Claim 1: "...***to a pore depth from the surface of the semiconductor of at least 5 microns***..."

No basis for such teaching can be found in the original disclosure. On the contrary, the original application teaches to impregnate the beneficial organic substance to a pore depth from the surface of the material of ***at least 50 microns, preferably at least 100 microns, especially at least 150 microns*** (cf. paragraph bridging description pages 12 and 13) .

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 16, 17 and 37-41 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(I) PCT).

Re Item V
Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following document/s/:

D1: US 2003/170280 A1 (CANHAM LEIGH T ET AL) 11 September 2003

D2: US 2003/134424 A1 (CANHAM LEIGH T ET AL) 17 July 2003

D3: WO 02/067998 A (PSIMEDICA LIMITED; CANHAM, LEIGH, TREVOR; ASTON, ROGER) 6 September 2002

D4: WO 03/011251 A (PSIMEDICA LIMITED; CANHAM, LEIGH, TREVOR; ASTON, ROGER) 13 February 2003

D5: KARLSSON L M ET AL: "Penetration and loading of human serum albumin in porous silicon layers with different pore sizes and thicknesses." JOURNAL OF COLLOID AND INTERFACE SCIENCE. 1 OCT 2003, vol. 266, no. 1, 1 October 2003 (2003-10-01), pages 40-47, XP002318975 ISSN: 0021-9797

D6: FORAKER AMY B ET AL: "Microfabricated porous silicon particles enhance paracellular delivery of insulin across intestinal Caco-2 cell monolayers." PHARMACEUTICAL RESEARCH. JAN 2003, vol. 20, no. 1, January 2003 (2003-01), pages 110-116, XP002318976 ISSN: 0724-8741

The composition according to independent claim 1 is not novel (Art.33(2) PCT) in view of prior art disclosures which can be taken from D5 and D6. D5 discloses porous silicon particles impregnated with human serum albumin and showing loading capacities of up to 2.6 mg protein per mg porous silicon (cf. page 44). D6 discloses porous silicon particles impregnated with insulin and a permeation enhancer such as sodium laurate or sodium caprate. Different amounts of said permeation enhancers are loaded into the silicon particles, e.g. up to 0.674 µg sodium laurate per particle (cf. Fig. 6). With an average particle weight of approximately 1 µg (cf. Table I) this corresponds to an impregnation of up to 67% by weight.

The method and use according to independent claims 37 and 41 are not novel (Art. 33(2) PCT) in view of prior art disclosures which can be taken from D3 and D6.
D3 (cf. page 20, lines 11-15 ; claim 12) discloses a method for optimising therapeutic effect and targeting of anti-cancer drugs to tumour tissue using drug loaded silicon carriers. It should be noted that the method of D3 implicitly improves bioavailability of the drug, since drug delivery remains localised at the target tissue and therapeutic effect is optimised. D6 (cf. page 116, last paragraph) shows that drug permeation rates across Caco-2 cell monolayers (as model for intestinal epithelial cells) can be enhanced significantly using porous silicon particles as delivery vehicles. Hence, also the method of D6 suggests improvement of bioavailability.

The impregnation methods according to independent claims 18 and 25 are not considered to involve an inventive step (Art. 33(3) PCT) in view of prior art teaching which can be taken from D1-D6. Methods of impregnation of the organic substance in molten state, i.e. above melting point, are disclosed e.g. D1 (e.g. paragraph [0225]) and D2 (e.g. paragraph [0200]). Although the methods disclosed in D1 and D2 do not explicitly mention the loading of more than 15% of organic substance, this feature is not considered to involve an inventive step, since it is obvious to the skilled person that such loading capacity may easily be achieved, especially when considering the disclosures of D5 and D6, which show loading capacities of much higher than 15%.
Methods of impregnation of the organic substance in solution, i.e. dissolved in an appropriate solvent, are disclosed e.g. in D2 (e.g. paragraph [0200]), D3 (e.g. page 27, lines 23-28), D4 (e.g. page 9, line 36 - page 10, line 8), D5 (e.g. page 41, right column, last paragraph) and D6 (e.g. page 111, left column, last paragraph). Although the described methods do not mention impregnation at a specific temperature of 40°C or higher, this feature is not considered to involve an inventive step, because at least it is suggested by D6 (cf. page 111, left column, last paragraph), which teaches to keep solutions comprising e.g. C12-compounds at a temperature of > 37°C to prevent solidification before loading. Accordingly, it is obvious to the skilled person to choose the appropriate temperature to reduce viscosity or at least avoid solidification in order to improve impregnation of the solution by capillary action.

In view of the state of the art disclosed in D1-D6, also the dependent claims 3-17, 19-24, 26-36 and 38-40 do not appear to contain any additional features which, in combination with the features of any claim to which they refer, would render the claimed subject-matter novel and/or inventive (Art.33(2)-(3) PCT). The specific embodiments are known or at least suggested by the cited state of the art. Loading of organic substance into porous silicon particles or implants is disclosed by all documents D1-D6. Although D1-D4 do not specifically disclose loading capacities of the organic substances into the silicon particles, it is known from D5 and D6 that high loadings can be achieved. None of the claimed features appears to bring a solution to any specific problem, as compared to the state of the art, which solution would involve an inventive step.

The subject-matter of claim 2 is considered to meet the requirements of novelty and inventive step (Art. 33(2)(3) PCT). Impregnation of a beneficial organic substance to a

pore depth from the surface of a semiconductor of at least 50 microns is not disclosed nor suggested by any of the prior art documents. As discussed in the pending application, such impregnated semiconductors are advantageous as the high loading levels mean that the composition can be administered fewer times yet will still deliver the desired high dose in a controlled manner. The high pore filling levels mean that high loading can be achieved with very little of the beneficial substance being wasted.

The compositions and the processes of preparation thereof as defined in claims 1-15 and 18-36 are considered to be industrially applicable and accordingly meet the requirements of Art.33(4) PCT.

Claims

1. A composite material comprising a porous semiconductor impregnated with at least one beneficial organic substance to a pore depth from the surface of the semiconductor of at least 5 microns, wherein the beneficial organic substance is present in an amount of at least 15 % by weight, based on the weight of the material.

2. A material according to claim 2 wherein the porous semiconductor is impregnated with at least one beneficial organic substance to a pore depth from the surface of at least 50 microns.

3. A material according to claim 1 or claim 2 wherein the porous semiconductor is doped or undoped silicon, germanium, silicon carbide or silicon nitride

4. A material according to claim 3 wherein the porous semiconductor is silicon

5. A material according to claim 4 wherein the silicon is resorbable

6. A material according to claim 5 where the silicon is mesoporous

7. A material according to any of claims 4 to 6 wherein the porous silicon has a porosity of from 40% to 90%

8. A material according to any preceding claim wherein the beneficial organic substance has a solubility in aqueous media of no more than 10mg/mL at a pH range 1-7.

9. A material according to any preceding claim wherein the beneficial organic substance has a melting point of below 300°C.

10. A material according to claim 9 wherein the beneficial organic substance has a melting point of below 100°C

11. A material according to any preceding claim wherein the beneficial organic substance is selected from chlorambucil, amitriptyline, ibuprofen , procaine, levamisole, plumbagin, cyclophosphamide, busulfan, dexamethasone , lauric acid, medroxy progesterone acetate, vitamin K, vitamin E, paclitaxel and rifampicin or a mixture thereof.

12. A material according to any preceding claim wherein the beneficial organic substance is present in an amount of from 15% to 85% by weight, based on the weight of the material.

13. A material according to any preceding claim wherein the beneficial organic substance is distributed substantially uniformly through the pores of the semiconductor.

14. A pharmaceutical composition comprising a material according to any preceding claim

15. A pharmaceutical composition according to claim 14 in the form of an implant or particles.

16. Use of a material according to any of claims 1 to 13 or a composition according to claim 14 or claim 15 in therapy

17. A method of delivering a beneficial substance to a patient in need thereof comprising delivering to the patient a composition according to claim 14 or claim 15.

18. A method for preparing a composite material comprising a porous semiconductor impregnated with at least one beneficial organic substance, wherein the beneficial organic substance is present in an amount of at least 15% by weight based on the weight of the composite material, comprising the steps of:-

i) bringing the beneficial organic substance into contact with the porous semiconductor; and

ii) allowing the beneficial organic substance to impregnate the porous semiconductor, the impregnation being performed at a temperature which is at or above the melting point of the beneficial organic substance.

19. A method according to claim 18 wherein the impregnation is brought about by the steps of:-

i) heating the porous semiconductor to a temperature at or above the melting point of the beneficial organic substance;

ii) bringing the beneficial organic substance into contact with the heated porous semiconductor, thereby causing the beneficial organic substance to become molten; and

iii) allowing the molten beneficial organic substance to impregnate the porous semiconductor.

20. A method according to claim 18 wherein the impregnation is brought about by the steps of:-

i) heating the beneficial organic substance to a temperature at or above its melting point, thereby causing the beneficial organic substance to become molten ;

ii) bringing the molten beneficial organic substance into contact with the porous semiconductor; and

iii) allowing the molten beneficial organic substance to impregnate the porous semiconductor.

21. A method according to claim 18 wherein both the porous semiconductor and the beneficial organic substance, independently, are heated to a temperature at or above the melting point of the beneficial organic substance and then brought into contact together to allow impregnation to occur.

22. A method according to any one of claims 18 to 21 wherein the impregnation is performed at a temperature of from 40°C to 200°C.

23. A method according to claim 22 wherein the impregnation is performed at a temperature of from 60°C to 130°C

24. A method according to any one of claims 18 to 23 wherein the impregnation is performed at a temperature of from 5°C to 15°C above the melting point of the beneficial organic substance.

25. A method for preparing a composite material comprising a porous semiconductor impregnated with at least one beneficial organic substance, wherein the beneficial organic substance is present in an amount of at least 15% by weight based on the weight of the composite material, comprising the steps of:-

i) dissolving the beneficial organic substance in a solvent for the beneficial organic substance;

ii) bringing the solution of part(i) into contact with the porous semiconductor ; and

iii) allowing the beneficial substance to impregnate the porous semiconductor, the impregnation being performed at a temperature in the range of from 40°C to 200°C .

26. A method according to claim 25 wherein the impregnation is performed at a temperature of from 60°C to 130°C

27. A method according to claim 25 or 26 wherein the impregnation is performed at a temperature which is at or above the boiling point of the solvent for the beneficial substance

28. A method according to any one of claims 25 to 27 wherein the impregnation is performed at a temperature which is at or above the melting point of the beneficial organic substance.

29. A method according to any one of claims 25 to 28 wherein the impregnation is brought about by the steps of:-

i) dissolving the beneficial organic substance in a solvent for the beneficial organic substance;

ii) heating the porous semiconductor to the temperature at which impregnation is to be performed;

iii) bringing the solution of part(i) into contact with the heated porous semiconductor ; and

(iv) allowing the beneficial substance to impregnate the porous semiconductor

30. A method according to any one of claims 25 to 28 wherein the impregnation is brought about by the steps of:-

i) dissolving the beneficial organic substance in a solvent for the beneficial organic substance;

ii) heating the solution of part (i) to the temperature at which impregnation is to be performed;

iii) bringing the heated solution of part(ii) into contact with the porous semiconductor ; and

(iv) allowing the beneficial substance to impregnate the porous semiconductor

31. A method according to any one of claims 25 to 28 wherein both the porous semiconductor and the solution of beneficial organic substance, independently, are heated to the temperature at which impregnation is to be performed and are brought into contact together to allow impregnation to occur.

32. A method according to any of claims 18 to 31 wherein the semiconductor is silicon

33. A method according to any of claims 18 to 32 wherein the beneficial organic substance has a melting point of below 300°C

34. A method according to any of claims 18 to 33 wherein the beneficial organic substance is selected from chlorambucil, amitriptyline, ibuprofen , procaine, levamisole, plumbagin, cyclophosphamide, busulfan, dexamethasone , lauric acid, medroxyprogesteron acetate, vitamin K, vitamin E, paclitaxel and rifampicin or a mixture thereof.

35. A method according to any of claims 18 to 34 wherein the porous semiconductor is heated to a temperature of from 100°C to 250°C prior to being brought into contact with the beneficial organic substance.

36. A method according to any one of claims 18 to 35 wherein the porous semiconductor and beneficial organic substance are maintained in contact for a period of from 1 minute to 2 hours.

37. A method of enhancing the bioavailability of a beneficial organic substance on administration to a subject comprising, impregnating a porous semiconductor with said beneficial organic substance and delivering the impregnated material to the subject.

38. A method according to claim 37, wherein the semiconductor is silicon.

39. A method according to claim 38, wherein the porous silicon has a porosity of from 40% to 90%.

40. A method according to any of claims 37 to 39, wherein the beneficial organic substance has a solubility in aqueous media of no more than 10 mg/ml at a pH in the range 1-7.

41. Use of a material comprising a porous semiconductor impregnated with a beneficial organic substance to deliver said beneficial organic substance to a subject in order to enhance the bioavailability of the beneficial organic substance on administration to the subject.